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| EXAMINER | |
|---|---|
| KEMMERER, ELIZABETH | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/541,953 | JO, HANJOONG | |
| | Examiner | Art Unit | |
| | Elizabeth C. Kemmerer, Ph.D. | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4,5 and 7-33* is/are pending in the application.

4a) Of the above claim(s) *7-12 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,13-16,29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments, And/Or Claims*

The amendment of 28 October 2008 has been entered in full. Claims 3 and 6 are canceled. Claims 7-12 and 17-28 remain withdrawn from consideration for reasons of record. Claims 1, 2, 4, 5, 13-16, and 29-33 are under examination.

### *Withdrawn Objections And/Or Rejections*

The requirement for a new title and the objection to the disclosure for informalities as set forth at p. 3 of the previous Office Action (mailed 28 May 2008) is *withdrawn* in view of the amendments to the specification submitted 28 October 2008.

The rejection of claim 29 under 35 U.S.C. § 112, second paragraph, as set forth at pp. 3-4 of the previous Office Action (mailed 28 May 2008) is *withdrawn* in view of the amendments to the claims submitted 28 October 2008.

### *Claim Objections*

Claim 29 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Dependent claim 29 is now clearly limited to a pharmaceutical composition comprising an antagonist which is a nucleic acid. However, claim 1 (from which claim 29 depends) is directed to a pharmaceutical composition comprising an antagonist or prodrug thereof which has the

activity of interfering with or reducing binding of bone morphogenic protein or a fragment thereof to a bone morphogenic protein receptor. Nucleic acids do not have such an activity. Rather, pharmaceutical compositions comprising nucleic acids act via increasing or decreasing *expression* of a protein, and *not* by increasing or decreasing *binding activity.* Therefore, claim 29 now clearly fails to further limit claim 1.

Amending claim 29 to recite either of the following would be remedial:

29. (Amended) The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises a bone morphogenic protein antagonist or a prodrug thereof that includes the protein encoded by the nucleic acid sequence of SEQ ID NO: 1.

29. (Amended) The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises a bone morphogenic protein antagonist or a prodrug thereof that includes chordin.

Claims 1 and 30 are objected to because of the following informalities: Claim 1 recites "…**a** vascular cell bone morphogenic receptor**s**…" which is grammatically incorrect. Amending the claim so that "receptors" is singular would be remedial. Claim 30 misspells "chordin." Appropriate correction is required.

***35 U.S.C. § 112, First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 13-16, and 29-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed invention wherein the active agent is a bone morphogenic protein-4 antagonist or a bone morphogenic protein-4 receptor antagonist, does not reasonably provide enablement for the claimed invention wherein the active agent inhibits other bone morphogenic proteins or other bone morphogenic protein receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pp. 4-6 of the previous Office Action (mailed 28 May 2008). Specifically, while the claims have been amended to recite bone morphogenic protein-4, the claims still broadly recite any vascular cell bone morphogenic protein receptor. The specification only discloses that bone morphogenic protein-4 receptor is present on vascular cells. The claims also continue to recite prodrugs, while the specification fails to disclose a single species of prodrug.

Applicant's arguments (pp. 8-9, remarks received 28 October 2008) have been fully considered but are not found to be persuasive. Specifically, Applicant argues that the claim amendments overcome the rejection. However, as stated above, the claims still encompass pharmaceutical compositions comprising a bone morphogenic protein receptor antagonist or prodrug thereof wherein the bone morphogenic receptor is defined as a vascular cell bone morphogenic protein receptor. The claims are not limited to BMP-4 receptors as set forth in the instant rejection.

Due to the large quantity of experimentation necessary to determine which bone morphogenic protein receptors other than BMP-4 receptors are present and active on vascular cells, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which provides no guidance regarding what BMP receptors are present and active on vascular cells, the unpredictability of what protein is expressed by any particular cell type without assaying for their presence, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 29 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 29 is directed to a genus of compositions including the nucleic acid of SEQ ID NO: 1 that inhibits binding of BMP-4 to its receptor. There is no disclosure of any species of such a nucleic acid composition having the required activity. Indeed, nucleic acids cannot have the activity of inhibiting binding of a polypeptide to its receptor. The only possible activity is to increase or decrease expression of a polypeptide. New claim 31 is directed to a composition comprising a carboxy-terminal fragment of noggin, chordin, DAN, or veinless, which is 10-200

residues in length. While literal support for these words can be found at the bottom of p. 11, a representative number of species of such active antagonists have not been disclosed. In fact, it was known that the N-terminal fragment of noggin inhibits the binding of BMP-4 to its receptor, as acknowledged by the specification at p. 11. However, neither the specification nor the prior art provides adequate written description of a representative number of species of C-terminal fragments as small as 10 residues in length that have the required activity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a general recitation of C-terminal fragment lengths and a requirement for an antagonistic activity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.)

The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 (BPAI 1993). In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 13, 14, 16, 32, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/56879 (Weber et al.; published 28 September 2000) for reasons of record. Furthermore, regarding new claims 32 and 33, it is noted that Weber et al.'s modified BMP-4 inherently has a cysteine knot formation. For example, see p. 7, second paragraph wherein preferred antagonists are described as those with N-terminal extensions. Such would still have the native cysteine knot structure at the C-terminus.

Applicant's arguments (pp. 9-10, remarks received 28 October 2008) have been fully considered but are not found to be persuasive. Specifically, Applicant argues that Weber et al. is directed to treatment of heterotopic calcification. Applicant argues that the antagonists taught by Weber et al. are cytokines and not modified BMPs or prodrugs thereof. Applicant points to pp. 1 and 6 of Weber et al. This has been fully considered but is not found to be persuasive. Weber et al. specifically teach modified BMP-5 polypeptides at p. 7, wherein a preferred embodiment is an N-terminally extended BMP. See also p. 10, second paragraph.

Applicant argues that Weber et al. fail to address the problem addressed by Applicant, i.e., vascular inflammation. Applicant takes issue with the examiner's statement that the receptors taught by Weber et al. are inherently vascular cell bone morphogenic protein receptors. This has been fully considered but is not found to be persuasive. Weber et al. disclose a modified BMP-4 which inhibits the binding of BMP-4 to its receptor. See p. 10, second paragraph. See also pp. 15-16, wherein Weber et

al. disclose that BMP-4 plays an important role in vascularization, and that the BMP-4 antagonists disclosed therein can be used to inhibit vascularization. Therefore, Weber et al. specifically teach that their BMP-4 antagonists are to be administered at a site wherein vascular cells are present. Therefore, they would inherently have the activity required in the claims. It is important to note that the claims and specification indicate that the inhibition or reduction in vascular inflammation occurs as a result of the antagonist interfering with or reducing the binding of BMP to its receptors. This is precisely what the BMP-4 antagonist of Weber et al. does, and thus it inherently has the required activity.

Claims 1, 4, 5, 13, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by De Robertis et al. (US 5679783; issued 21 October 1997) for reasons of record. Additionally, regarding new claim 30, N-terminal and C-terminal fragments of chordin are taught at col. 2-3. De Robertis et al. teach that the carboxy-terminal fragment is the mature, active protein. See col. 5, second paragraph.

Applicant's arguments (pp. 9-10, remarks received 28 October 2008) have been fully considered but are not found to be persuasive. Specifically, Applicant argues that De Robertis et al. fail to teach vascular inflammation. Applicant again takes issue with the examiner's explanation that the receptors taught by De Robertis et al. are inherently vascular cell bone morphogenic receptors. Applicant characterizes De Robertis et al. as generally being directed to growth factors, neurotrophic factors, and their inhibitors. Applicant urges that De Robertis et al. is mostly directed to chordin, and fails to disclose

fragments of chordin as claimed. This has been fully considered but is not found persuasive. As discussed in the previous Office Action, De Robertis et al. teach a pharmaceutical composition comprising chordin or a fragment thereof in combination with a pharmaceutically acceptable carrier at col. 2, li. 65, col. 3, li. 9-13, and paragraph bridging col. 8-9. De Robertis et al. explicitly teach that chordin is a BMP-4 antagonist that inhibits binding of BMP-4 to its receptor at the paragraph bridging col. 6-7. Therefore, the chordin composition of De Robertis et al. inherently has the activity recited in the claims because it inhibits binding of BMP-4 to its receptor.

***35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/56879 (Weber et al.; published 28 September 2000) in view of Hunter et al. (US 5716981; issued 10 February 1998) for the reasons set forth at pp. 8-9 of the previous Office Action (mailed 28 May 2008).

Applicant argues (p. 11, remarks received 28 October 2008) that claim 15 is allowable for the same reasons as claim 14. This has been fully considered but is not found to be persuasive for the reasons given above and in the previous Office Action.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ECK/
06 January 2009

/Elizabeth C. Kemmerer/
Elizabeth C. Kemmerer, Ph.D.
Primary Examiner, Art Unit 1646